FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: SCH 1808

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371

U.S. APPLICATION NO. (If known, see 37 CFR §1.5): 09/807402

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/IB99/07111	13 OCTOBER 1999	14 OCTOBER 1998

TITLE OF INVENTION: COMBINATION OF GESTAGENS AND SUGARS

APPLICANT(S) FOR DO/EO/US: HOFERT, Peter, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/807402	PCT/EP99/07711	SCH 1808

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):		
Search Report has been prepared by the EPO or JPO $860.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482) $690.00		
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2)) $710.00		
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO $1000.00		
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).		

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	- 20 =	0	x $ 18.00	$0.00	
Independent claims	- 3 =	0	x $ 80.00	$0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00		
TOTAL OF ABOVE CALCULATIONS =				$860.00	
Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).					
SUBTOTAL =				$860.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).					
TOTAL NATIONAL FEE =				$860.00	
Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.					
TOTAL FEES ENCLOSED =				$860.00	
				Amount to be refunded:	
				charged:	

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO: Customer Number 23,599

23599
PATENT TRADEMARK OFFICE

SIGNATURE

Anthony J. Zelano
NAME

27,969
REGISTRATION NUMBER

Filed: 13 APRIL 2001

AJZ:kms

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP99/07711
International Filing Date	:	13 OCTOBER 1999
Priority Date(s) Claimed	:	13 OCTOBER 1998
Applicant(s) (DO/EO/US)	:	HOFERT, Peter, et al.

Title: COMBINATION THAT CONSISTS OF NORPREGNANE DERIVATIVES AND CYCLODEXTRIN

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

4. (Amended) Combination according to claim 1, whereby the cyclodextrin is a β-cyclodextrin.

5. (Amended) Combination according to claim 1, whereby the cyclodextrin and the gestagen

are present with β-cyclodextrin in a complex of 1:n (gestagen : cyclodextrin, n ≥ 1), and

are present with γ-cyclodextrin in a complex of 1:n (n ≥ 1) (gestagen : cyclodextrin).

6. (Amended) Combination according to claim 1 as a pharmaceutical agent.

8. (Amended) Combination according to claim 6 for the production of a pharmaceutical agent for treating menopausal symptoms.

9. (Amended) Combination according to claim 1 for birth control.

10. (Amended) Pharmaceutical agent or pharmaceutical preparation that contains a combination according to claim 1 with pharmaceutically compatible adjuvants and vehicles.

11. (Amended) Pharmaceutical agent or pharmaceutical preparation that contains a combination according to claim 1 for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

12. (Amended) Use of a combination according to claim 1 for the production of a medication for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia.

13. (Amended) Process for birth control with administration of a combination according to claim 1.

15. (Amended) Process for complexing a gestagen according to claim 1 and a β-cyclodextrin or γ-cyclodextrin while being triturated as a dry mixture or by precipitation reaction, preferably co-precipitation.

16. (Amended) Process for direct pelletizing of a gestagen complex according to claim 1 with a β-cyclodextrin or γ-cyclodextrin with the addition of pharmaceutically compatible adjuvants.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings to Show Changes Made**".

Respectfully submitted,

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AJZ:jmm

FILED: 3 AUGUST 2001

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 4-6, 8-13 and 15-16 have been amended as follows:

4. (Amended) Combination according to ~~one of the preceding~~ claims 1, whereby the cyclodextrin is a β-cyclodextrin.

5. (Amended) Combination according to ~~one of the preceding~~ claims 1, whereby the cyclodextrin and the gestagen

are present with β-cyclodextrin in a complex of 1:n (gestagen : cyclodextrin, n ≥ 1), and

are present with γ-cyclodextrin in a complex of 1:n (n ≥ 1) (gestagen : cyclodextrin).

6. (Amended) Combination according to ~~one of the preceding~~ claims 1 as a pharmaceutical agent.

8. (Amended) Combination according to claim ~~6 or 7~~ for the production of a pharmaceutical agent for treating menopausal symptoms.

9. (Amended) Combination according to ~~one of the preceding~~ claims ~~1 to 5~~ for birth control.

10. (Amended) Pharmaceutical agent or pharmaceutical preparation that contains a combination according to ~~one of the preceding~~ claims 1 with pharmaceutically compatible adjuvants and vehicles.

11. (Amended) Pharmaceutical agent or pharmaceutical preparation that contains a combination according to ~~one of the preceding~~ claims 1 for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

12. (Amended) Use of a combination according to ~~one of the preceding~~ claims ~~1 to 9~~ for the production of a medication for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia.

13. (Amended) Process for birth control with administration of a combination according to ~~one of~~ claims ~~1 to 9~~.

15. (Amended) Process for complexing a gestagen according to ~~one of~~ claims ~~1 and 2~~ and a β-cyclodextrin or γ-cyclodextrin while being triturated as a dry mixture or by precipitation reaction, preferably co-precipitation.

16. (Amended) Process for direct pelletizing of a gestagen complex according to ~~one of~~ claims 1 ~~and 2~~ with a β-cyclodextrin or γ-cyclodextrin with the addition of pharmaceutically compatible adjuvants.

COMBINATION THAT CONSISTS OF NORPREGNANE DERIVATIVES AND CYCLODEXTRIN

The invention relates to a combination that consists of at least one gestagen and a sugar. The sugar stabilizes the gestagen to the extent that the acyloin rearrangement in the side chain at atoms C_{20} and C_{21} as well as oxidative decomposition are prevented. In addition, the invention also comprises the use of the combination as pharmaceutical agent and process for the production of combinations.

Prior Art

Complexes that consist of steroidal sex hormones and cyclodextrin are known from WO 96/02277 (date of application: July 10, 1996). Only the complex that consists of 17α-ethinylestradiol and ß-cyclodextrin is actually described.

In general, gestagens are described in publication WO 96/20209 with the application date of July 4, 1996. In this case, in particular a (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione is also mentioned. Gestagens are used for the treatment of menopausal symptoms. Fertility can also be controlled with these gestagens.

Gestagens with an α-hydroxyketone structure in the side chain are subject to an acyloin rearrangement during storage. In this case, steric variants occur. This rearrangement is

accelerated by many pharmaceutical adjuvants (e.g., lactose, magnesium stearate).

Moreover, oxidation reactions occur in various molecular positions.

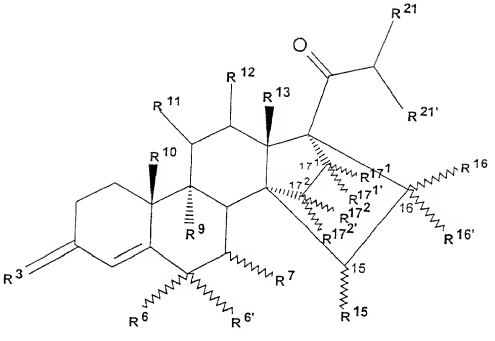
Object and Solution

The object is thus to protect gestagens, especially (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione, from decomposition by acyloin rearrangement or oxidation without having a negative effect on the pharmacological compatibility and pharmaceutical processing.

The object is achieved by a combination that consists of at least one gestagen and a ß-cyclodextrin or γ-cyclodextrin, or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins,

whereby the gestagens are 14,17-C_2-bridged steroids, which belong

to the group of formula I:



(I)

in which

R^3 stands for an oxygen atom, the hydroxyimino group or two hydrogen atoms,

R^6 stands for a hydrogen, fluorine, chlorine or bromine atom or for an α- or ß-position C_1-C_4 alkyl radical, whereby then $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ stands for a hydrogen, fluorine, chlorine or bromine atom or for a C_1-C_4 alkyl radical, whereby then $R^{6'}$ and R^7 represent a common additional bond,

R^7 stands for an α- or ß-position C_1-C_4 alkyl radical, whereby then R^6 and $R^{6'}$ represent hydrogen atoms, or else

R^6 and R^7 together stand for an α- or ß-position methylene group, and $R^{6'}$ stands for a hydrogen atom, or

R^6 and $R^{6'}$ together stand for an ethylene group or a methylene group, and R^7 stands for a hydrogen atom,

R^9 and R^{10} in each case stand for a hydrogen atom or a common bond,

R^{11} and R^{12} in each case stand for a hydrogen atom or a common bond,

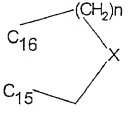
R^{13} stands for a methyl or ethyl group,

R^{15} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

R^{16} and $R^{16'}$, independently of one another, stand for a hydrogen atom, a C_1-C_3 alkyl radical or a C_2-C_4 alkenyl radical or together for a C_1-C_3 alkylidene group,

R^{15} and R^{16} stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a C_1-C_3 alkyl radical, or

R^{15} and R^{16} together stand for a ring of partial formula



in which n = 1 and 2, and X means a methylene group or an oxygen atom, and

$R^{16'}$ stands for a hydrogen atom,

R^{171} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

R^{172} stands for a hydrogen atom, a C_1-C_3 alkyl radical, or a C_2-C_4 alkenyl radical,

$R^{171'}$ and $R^{172'}$ in each case stand for a hydrogen atom or for a common bond,

R^{21} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

$R^{21'}$ stands for a hydrogen atom, a C_1-C_3 alkyl radical, or a hydroxy group.

The wavy lines ∿∿∿ in the general formulas of this invention mean that the substituent in question can be found in α- or ß-position at the corresponding carbon atom.

The C_1-C_3 alkyl groups that are mentioned above as possible substituents can be a methyl, ethyl, n-propyl or i-propyl group, and the C_1-C_4 alkyl groups in addition can be an n-butyl, i-butyl or tert-butyl group. A methyl group or ethyl group is preferred in all cases.

In the case of the C_2-C_4 alkenyl radical for R^{16}, $R^{16'}$ and/or R^{172}, this is a vinyl, allyl or but-3-enyl radical; the vinyl radical is preferred.

Special Gestagens:

Preferred according to this invention are combinations that consist of at least one gestagen and a ß-cyclodextrin or γ-cyclodextrin, or derivatives of these cyclodextrins, which are

obtained by etherification or esterification of free alcoholic functions of cyclodextrins,

whereby the gestagens belong to the group of formula I:

in which

R^3 stands for an oxygen atom or two hydrogen atoms, and/or

R^6 stands for a hydrogen atom or for an α-position or ß-position C_1-C_4 alkyl radical,

if $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ stands for a hydrogen, chlorine or bromine atom or for a C_1-C_4 alkyl radical,

if $R^{6'}$ and R^7 represent a common additional bond, and/or

R^{16} and $R^{16'}$ in each case stand for a hydrogen atom, in each case for a methyl group or one of these two substituents stands for a C_1-C_4 alkyl group or a vinyl group, and the other of these two substituents stands for a hydrogen atom, or both together form a C1-C3-alkenyl group, and/or

R^{171} and R^{172}, independently of one another, stand for a hydrogen atom or a methyl group, and/or

$R^{171'}$ and $R^{172'}$ in each case stand for a hydrogen atom or a common bond, and/or

R^{21} stands for a hydrogen atom or a C_1-C_3 alkyl radical, and $R^{21'}$ stands for a hydrogen atom or a hydroxy group,

and the other substituents all can have the meanings that are indicated in formula (I).

More preferred are combinations that consist of at least one gestagen and a ß-cyclodextrin or γ-cyclodextrin, or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins, whereby the gestagen belongs to the group of the following substances:

14,17-Ethano-19-norpregna-4,9-diene-3,20-dione;

14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

14,17-ethano-19-norpregna-4,15-diene-3,20-dione

14,17-ethano-19-norpregna-4,6,15-triene-3,20-dione

14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

21-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

21-methyl-14,17-ethano-19-norpregna-4,15-diene-3,20-dione

21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

14,17-etheno-19-norpregn-4-ene-3,20-dione;

14,17-etheno-19-norpregna-4,6-diene-3,20-dione;

14,17-etheno-19-norpregna-4,9-diene-3,20-dione;

21-methyl-14,17-etheno-19-norpregn-4-ene-3,20-dione

21-methyl-14,17-etheno-19-norpregna-4,6-diene-3,20-dione

21-methyl-14,17-etheno-19-norpregna-4,9-diene-3,20-dione;

21-methyl-14,17-etheno-19-norpregna-4,9,11-triene-3,20-dione

21-hydroxy-14,17-etheno-19-norpregn-4-ene-3,20-dione

21-hydroxy-14,17-etheno-19-norpregna-4,9-diene-3,20-dione

17^1-methyl-14,17-etheno-19-norpregn-4-ene-3,20-dione

17^1-methyl-14,17-etheno-19-norpregna-4,6-diene-3,20-dione

17^2-methyl-14,17-etheno-19-norpregn-4-ene-3,20-dione

17^2-methyl-14,17-etheno-19-norpregna-4,9-diene-3,20-dione

15ß,16α-dimethyl-14,17-etheno-19-norpregn-4-ene-3,20-dione

6-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

6-chloro-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

6α-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

6,21-dimethyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

15ß,16α-dimethyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

6-chloro-21-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

16α-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

16α-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

16α-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

16α,21-dimethyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

21-hydroxy-16α-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

16α-ethyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

16α-ethenyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

16-methyl-14,17-ethano-19-norpregna-4,15-diene-3,20-dione

(17^1R)-17^1-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

(17^1S)-17^1-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

(17^1R)-17^1-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17^1S)-17^1-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17^{2}R)-17^2-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione

(17^{2}R)-17^2-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

(17^{2}R)-17^2-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17^{2}R)-17^2,21-dimethyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

(17^{2}R)-17^2,21-dimethyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

(17^{2}R)-17^2,21-dimethyl-14,17-ethano-19-norpregna-4,9,11-triene-3,20-dione

16-methylene-14,17-ethano-19-norpregn-4-ene-3,20-dione

16-methylene-14,17-ethano-19-norpregna-4,6-diene-3,20-dione

16-methylene-14,17-ethano-19-norpregna-4,9-diene-3,20-dione

21-hydroxy-14,17-ethano-19-norpregn-4-ene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

21-hydroxy-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

(21R)-21-hydroxy-21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

(21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregn-4-ene-3,20-dione;

(21R)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

(21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9-diene-3,20-dione;

(21R)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

(21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,6-diene-3,20-dione;

(21R)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

(21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione

14,17-ethano-18a-homo-19-norpregn-4-ene-3,20-dione

14,17-ethano-18a-homo-19-norpregna-4,6-diene-3,20-dione

14,17-ethano-18a-homo-19-norpregna-4,9-diene-3,20-dione

14,17-ethano-18a-homo-19-norpregna-4,15-diene-3,20-dione

21-methyl-14,17-ethano-18a-homo-19-norpregn-4-ene-3,20-dione

21-methyl-14,17-ethano-18a-homo-19-norpregna-4,6-diene-3,20-dione

21-methyl-14,17-ethano-18a-homo-19-norpregna-4,9-diene-3,20-dione

(21R)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregn-4-ene-3,20-dione

(21S)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregn-4-ene-3,20-dione

(21R)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,9-ene-3,20-dione

(21S)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,9-ene-3,20-dione

(21R)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,6-ene-3,20-dione

(21S)-21-hydroxy-21-methyl-14,17-ethano-18a-homo-19-norpregna-4,6-ene-3,20-dione

Effectiveness of the Combination:

After oral administration, an equilibrium develops between the non-dissociated complex and the individual components at the gastrointestinal resorption site from the complex that consists of gestagen and a sugar derivative. In this case, by displacement of the gestagen from the complexing sugar derivative, the free active ingredient is quickly released and then resorbed. The sugar derivative, however, is not resorbed and is excreted unchanged via the intestine. The pharmacological effectiveness of the gestagen is described in WO096/20209.

In the gestagen receptor-binding test on gestagenic action with use of cytosol that consists of rabbit uterus homogenate and ^{3}H-progesterone as a reference substance, the gestagen shows a very strong affinity to the gestagen receptor. In the pregnancy maintenance test on the rat, the gestagens of general formula (I) show a very high gestagenic action.

In addition to very high gestagenic action in the pregnancy maintenance test, the gestagens of general formula I, in contrast to the already known compound 14,17-ethano-19-norpregn-4-ene-3,20-dione, however, for the most part also show a good gestagenic action after oral administration.

Based on their high gestagenic action, the gestagens of general formula (I) can be used, for example, by themselves or combined with estrogens in contraceptive preparations. All other

possible uses that are known for gestagens are also now options for the new complex, however.

The dose of the complexes according to the invention in contraceptive preparations is preferably to be 0.01 to 2 mg, calculated as free gestagen per day. Suitable doses can be determined routinely, for example by determining the bioequivalency compared to a known gestagen for a specific use, for example an amount that is bioequivalent to 0.030 to 0.150 mg of levonorgestrel for the contraception. This calibration also applies to the below-indicated doses regarding the gestagens.

The gestagenic and estrogenic active ingredient components are preferably administered together orally in contraceptive preparations. The daily dose is preferably administered one time. In addition to the oral administration, e.g., a transdermal administration is also possible.

As estrogens, preferably synthetic estrogens such as ethinylestradiol, 14α,17α-ethano-1,3,5(10)-estratriene-3,17ß-diol (WO 88/01275) or 14α,17α-ethano-1,3,5(10)-estratriene-3,16α,17ß-triol (Wo 91/08219) are also considered.

The estrogen is administered in an amount that corresponds to that of 0.01 to 0.05 mg of ethinylestradiol.

The new combinations that consist of at least one gestagen of formula I and a ß-cyclodextrin or γ-cyclodextrin, or derivatives of these cyclodextrins, can also be used in preparations for treating gynecological disorders and for substitution therapy. Because of their advantageous action profile, the combinations according to the invention are

especially well suited for treatment of premenstrual symptoms, such as headaches, depression, water retention and mastodynia. The daily dose in the treatment of premenstrual symptoms is approximately, for example, 1 to 20 mg, calculated as a free gestagen.

Finally, the new combinations can be used also as gestagenic components in the compositions that have become known recently for female birth control, which are distinguished by the additional use of a competitive progesterone antagonist (H. B. Croxatto and A. M. Salvatierra in Female Contraception and Male Fertility Regulation, ed. by Runnebaum, Rabe & Kiesel -- Vol. 2, Advances in Gynecological and Obstetric Research Series, Parthenon Publishing Group - 1991, page 245).

The dose lies in the range already indicated, and the formulation can be carried out as in conventional OC-preparations. The administration of the additional, competitive progesterone antagonist can also be performed sequentially in this case.

The formulation of the pharmaceutical preparations based on the new combinations is carried out in a way that is known in the art, by the active ingredient, optionally in combination with an estrogen, being processed with the vehicles, diluents, optionally flavoring correctives, etc., that are commonly used in galenicals and being converted into the desired form of administration.

For the preferred oral administration, especially tablets, coated tablets, capsules, pills, suspensions or solutions are suitable.

For the transdermal administration, especially matrix or membrane patches are suitable.

The combinations with compounds of general formula (I) can also be administered continuously by an intrauterine release system (IUD); the release rate of the active compound(s) is selected in this case so that the daily released dose lies within the dose ranges already indicated.

The production of the gestagens is described in more detail in WO 96/20209 (publication date July 4, 1996).

Preferred is a combination with the gestagen (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

Cyclodextrins:

ß-Cyclodextrin, γ-cyclodextrin and derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of cyclodextrins, are described in J. Pharm. Sci. 74 (1985), pp. 987-990 or Int. J. Pharm. 29 (1986), pp. 73-82.

More preferred is a combination that consists of a gestagen and a cyclodextrin, whereby the cyclodextrin is a ß-cyclodextrin.

Most preferred is the combination that consists of the gestagen (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin.

Advantages:

If gestagens, especially (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione, are mixed with adjuvants such as lactose, corn starch, mannitol, microcrystalline cellulose, polyvidone, hydroxypropylmethyl cellulose, dicalcium phosphate and maltodextrin, an accelerated degradation can be noted. In this connection, this is an acyloin rearrangement. There results a mixture that consists of two pairs of diastereomers with respectively exchanged positions of the keto group and the hydroxyl group at the C_{20} and C_{21} atom. From the four possible structures, only one corresponds to the above-mentioned substance (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

When stored at 25°C (60% relative humidity) over 3 months, the content of non-complexed (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione drops to below 90% of the starting value, if the substance is pelletized (i) either with the adjuvants lactose, corn starch, modified corn starch, polyvidone 25,000 and magnesium stearate (ii) or with the adjuvants with mannitol, hydroxypropylmethyl cellulose and magnesium stearate. The formulations of mannitol that can be pelletized directly with adjuvants (iii) or (iv) microcrystalline cellulose and magnesium stearate or (v) glyceryltribehenate also show a comparable degradation of the substance (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

By the combination according to the invention (complexing of the gestagen with ß-cyclodextrin), tablets can be obtained that

despite storage at critical temperatures have an active ingredient content that is still over 90% of the starting value in an open storage jar after 6 months of storage at 40°C, 75% relative humidity.

Additional Embodiments with Regard to Cyclodextrins

Advantageous is a combination according to the invention in which the cyclodextrin and the gestagen

are present with ß-cyclodextrin in a complex of 1:n (gestagen : cyclodextrin, n ≥ 1), a ratio of 1:2 (gestagen : cyclodextrin) is preferred, and

are present with γ-cyclodextrin also in a complex of 1:n (n ≥ 1) (gestagen : cyclodextrin); a ratio of 1:2 (gestagen : cyclodextrin) is preferred.

In addition to the increased shelf life, the stoichiometry of the complexing can be determined. In this case, it is obvious that the complexing in complexes (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and γ-cyclodextrin takes place at a ratio of 1:1 to 1:2 (gestagen : cyclodextrin). A complexing ratio of 1:2 (gestagen : cyclodextrin) is advantageous.

In the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin, a ratio of 1:2 (gestagen : cyclodextrin) is present.

Such complexes have a sometimes lower solubility product than the steroid by itself. The complexes thus can be produced by a precipitation reaction (e.g., co-precipitation).

Additional Embodiments as Pharmaceutical Agents

The combination according to the invention is preferred as a pharmaceutical agent. The action of the substances is described above (cf. WO96/20209).

More preferred is a pharmaceutical agent or a pharmaceutical preparation that contains a combination according to the invention, including pharmaceutical vehicles and adjuvants.

Still more preferred is a pharmaceutical agent or pharmaceutical preparation that contains a combination according to the invention for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

In addition, the invention relates to the use of the combinations according to the invention together with pharmacological adjuvants and vehicles, which are physiologically compatible, for the production of a medication for treating menopausal symptoms. Such adjuvants and vehicles are described in Remington's Pharmaceutical Science, 15th Ed. Mack Publishing Company, Easton, Pennsylvania (1980).

The combinations according to the invention show the action in the above-mentioned test at concentrations of 0.1 to 1000 ng/ml of the gestagen.

For the therapeutic action, the suitable dose is different and depends on, for example, the combinations that are used with

gestagens of general formula I, the host, the type of administration, and the type and the severity of the conditions to be treated. In general, however, satisfactory results can be expected in animals with daily doses of gestagens of 1 to 3000 µg/kg of animal body weight. In the case of larger mammals, for example humans, a recommended daily dose of gestagen is 0.1 to 200 mg. Preferred are values of 0.3 to 60 mg per day, more preferred 1 to 20 mg per day and most preferred 2 to 10 mg per day.

The invention additionally provides

(i) The use of one of the combinations according to the invention for the production of a medication for treating menopausal symptoms;

(ii) A process for treating menopausal symptoms; said process comprises an administration of a combination amount according to the invention, whereby the amount suppresses the disease, and whereby the combination amount is given to a patient who requires such a medication;

(iii) a pharmaceutical composition for treating menopausal symptoms; said treatment comprises one of the combinations according to the invention and at least one pharmaceutical adjuvant and/or vehicle.

The invention additionally provides

(i) The use of one of the combinations according to the invention for the production of a medication for

treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia;

(ii) a process for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia; said process comprises an administration of a combination amount according to the invention, whereby the amount suppresses the disease, and whereby the combination amount is given to a patient who requires such a medication;

(iii) a pharmaceutical composition for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia; said treatment comprises one of the combinations according to the invention and at least one pharmaceutical adjuvant and/or vehicle.

The daily dose in the treatment of premenstrual symptoms is approximately 1 to 20 mg, calculated as a free gestagen.

Additional Embodiments as an Oral Contraceptive Agent

The invention comprises a combination according to the invention for birth control.

Based on their high gestagenic action, the new combinations can be used with gestagens of general formula (I), for example by themselves or combined with estrogens in preparations for contraception. All other possible uses that are known for gestagens are also now options for the new compounds, however.

The dose of the combination according to the invention in contraceptive preparations is preferably to be 0.01 to 2 mg per day, calculated as free gestagen.

The gestagenic and estrogenic active ingredient components are preferably administered orally together in contraceptive preparations. The daily dose is preferably administered one time.

As estrogens, preferably synthetic estrogens such as ethinylestradiol, 14α,17α-ethano-1,3,5(10)-estratriene-3,17ß-diol (WO 88/01275) or 14α,17α-ethano-1,3,5(10)-estratriene-3,16α,17ß-triol (WO 91/08219) are considered.

The estrogen is administered in an amount that corresponds to that of 0.01 to 0.05 mg of ethinylestradiol.

Finally, the new combinations can also be used as gestagenic components in the compositions that have become known recently for female birth control, which are distinguished by the additional use of a competitive progesterone antagonist (H. B. Croxatto and A. M. Salvatierra in Female Contraception and Male Fertility Regulation, ed. by Runnebaum, Rabe & Kiesel -- Vol. 2, Advances in Gynecological and Obstetric Research Series, Parthenon Publishing Group - 1991, page 245).

The dose lies in the range already indicated, and the formulation can be carried out as in conventional OC-preparations. The administration of the additional, competitive progesterone antagonist can also be performed sequentially in this case.

Additional Embodiments as Stabilizing Processes

Advantageous is a process for stabilizing a gestagen according to Formula I with use of a ß-cyclodextrin or γ-cyclodextrin or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins. The preferred complex that consists of gestagen and cyclodextrin is the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin.

Preferred is a process for complexing a gestagen and a ß-cyclodextrin or γ-cyclodextrin while being triturated as a dry mixture. X-ray spectra of the powder, which was produced as a dry mixture, show that the complexing is already partially present but has not finished. This complexing is already surprising as a dry mixture.

More preferred is the production of complexes by precipitation reaction, e.g., co-precipitation, by an ethanolic solution of the gestagen being added in drops to an aqueous cyclodextrin solution. The complexes that consist of gestagens and cyclodextrin and that are produced by precipitation can be brought into the desired particle size distribution before being turned into pharmaceutical agents by suitable grinding techniques, e.g., that of air-jet grinding.

Preferred for production of the formulation is an encapsulation or granulation and subsequent pelletizing.

More preferred is a process for the direct pelletizing of the complex that consists of a gestagen with ß-cyclodextrin or γ-

cyclodextrin with the addition of pharmaceutically compatible adjuvants. In this case, a granulation step is eliminated. A granulation step involves the risk of the cyclodextrin complex being destroyed by the steroid being displaced from the cyclodextrin host by adjuvant molecules as guests.

Direct pelletizing was therefore performed with the addition of adjuvants of microcrystalline cellulose, lactose, croscarmellose-Na, highly dispersed silicon dioxide and magnesium stearate.

Example

The complexes that consist of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin and γ-cyclodextrin were produced in the following way:

19 mmol of the cyclodextrin was dissolved in 610 ml of water that is 45°C, and within 30 minutes, 7.6 mmol of ZK 187226, dissolved in 10 ml of ethanol, was added in drops. With another 5 ml of ethanol, it was flushed, allowed to cool to room temperature, stirred for 24 hours at room temperature, stirred for 2 hours in an ice bath (2°C), and the precipitate was suctioned off via a G2-frit. The complex that was obtained was then washed 2 more times with 50 ml of ice water each and once with ice-cold acetone. After drying in a desiccator on phosphorus pentoxide, the complex was characterized by Karl-Fischer-water determination, HPLC, DSC and x-ray powder diffractomy.

The fact that it is only after comparative trituration that a clear change is observed both in the x-ray powder spectrum and in the DSC indicates that a partial, but incomplete complexing already takes place in the trituration of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione with ß-cyclodextrin or γ-cyclodextrin.

After the complexes were ground, tablets were now produced from the produced cyclodextrin complexes of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione. For pelletizing, it is important that it is performed as direct

pelletizing, without a granulation step. Such a granulation process would namely involve the risk of the cyclodextrin complexes being destroyed by (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione being displaced from the cyclodextrin host by adjuvant molecules as guests.

Direct pelletizing would therefore be performed with the addition of adjuvants of microcrystalline cellulose, lactose, croscarmellose-Na, highly dispersed silicon dioxide and magnesium stearate.

The tablets that are produced as well as a formulation that is produced from non-complexed active ingredient and the complexes that consist of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin and γ-cyclodextrin were stored to test shelf life, and the content of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione (in the tablets relative to the nominal content of 0.1 mg of active ingredient per tablet, in the complexes as percent by weight) was determined after 1.5-month and 3-month storage. The results are shown in Tables 1 to 5.

In comparison to the tablets produced with an uncomplexed active ingredient, the tablets produced from the ß-cyclodextrin clathrates and γ-cyclodextrin clathrates show a considerably improved shelf life. The ß-cyclodextrin clathrate shows the best stabilization, can be produced in good quality and is also economically more advantageous compared to γ-cyclodextrin. Based on the results of the 3-month storage, an adequate shelf life for a market formulation results for the tablets that are produced

with the complex that consists of (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione and ß-cyclodextrin.

Table 1: ß-Cyclodextrin-Clathrate Tablets

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	97.0% (1.0%)	-	-	-	-	-	-
1.5	97.4% (0.8%)	97.0% (0.6%)	96.7% (0.7%)	95.5% (1.8%)	93.5% (0.9%)	92.9% (0.7%)	89.7% (0.8%)
3	97.0% (0.8%)	97.1% (1.0%)	96.6% (0.7%)	95.2% (0.5%)	91.8% (1.0%)	92.6% (1.2%)	89.0% (1.7%)

[Key to Table 1:]

Monate = months

60% r.F. = relative atmospheric humidity

Table 2: γ-CD-Clathrate Tablets

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	93.0% (8.3%)	-	-	-	-	-	-
1.5	97.9% (2.6%)	99.4% (2.5%)	98.8% (2.7%)	98.5% (3.6%)	95.1% (7.3%)	90.0% (4.7%)	85.1% (5.1%)
3	99.8% (4.2%)	96.5% (3.9%)	99.9% (5.7%)	97.9% (3.4%)	88.7% (3.0%)	77.1% (4.7%)	79.1% (1.6%)

[Key to Table 2:]

Monate = months

r.F. = relative atmospheric humidity

Table 3: (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,16-triene-3,20-dione Tablets

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	100.1% (0.8%)	-	-	-	-	-	-
1.5	nicht untersucht	90.6% (0.5%)	80.3% (0.3%)	26.6% (0.8%)	27.9% (1.1%)	0.3% (1.7%)	0.1% (14.3%)
3	101.2% (0.5%)	80.1% (0.6%)	63.9% (1.0%)	8.5% (5.2%)	14.1% (4.1%)	0.3% (68.0%)	0.1% (65.6%)

[Key to Table 3:]

Monate = months

r.F. = relative atmospheric humidity

nicht untersucht = not examined

Table 4: (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione-ß-cyclodextrin Complex Content in %

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	12.5% (0.3%)	-	-	-	-	-	-
1.5	12.5% (0.7%)	nicht untersucht	12.5% (0.4%)	nicht untersucht	12.4% (0.9%)	nicht untersucht	12.3% (0.8%)
3	12.5% (0.5%)	nicht untersucht	12.5% (0.3%)	nicht untersucht	12.6% (0.3%)	nicht untersucht	12.3% (0.5%)

[Key to Table 4:]

Monate = months

r.F. = relative atmospheric humidity

nicht untersucht = not examined

Table 5: (21S)-21-Hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione-γ-cyclodextrin Complex Content in %

Monate	-18°C	+25°C	+25°C, 60% r.F.	+40°C	+40°C, 75% r.F.	+60°C	+60°C, 75% r.F.
0	13.6% (2.8%)	-	-	-	-	-	-
1.5	13.8% (1.2%)	nicht untersucht	13.7% (0.8%)	nicht untersucht	13.3% (0.5%)	nicht untersucht	12.0% (1.3%)
3	13.9% (2.5%)	nicht untersucht	13.5% (1.3%)	nicht untersucht	13.0% (0.5%)	nicht untersucht	10.0% (1.1%)

r.F. = relative atmospheric humidity, set in the climatic chamber

[Key to Table 5:]

Monate = months

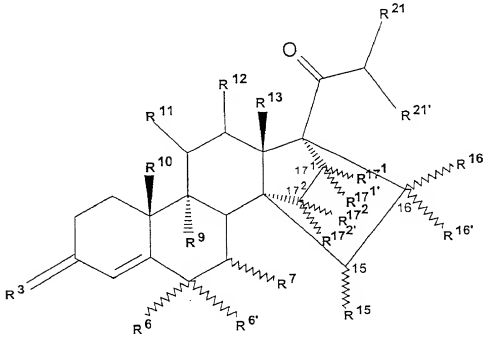
r.F. = relative atmospheric humidity

nicht untersucht = not examined

Claims

1. Combination that consists of at least one gestagen and a ß-cyclodextrin or γ-cyclodextrin or derivatives of these cyclodextrins, which are obtained by etherification or esterification of free alcoholic functions of the cyclodextrins, whereby the gestagen is a 14,17-C_2-bridged steroid.

2. Combination according to claim 1, whereby the gestagens belong to the group of formula I:



(I)

in which

R^3 stands for an oxygen atom, the hydroxyimino group, or two hydrogen atoms,

R^6 stands for a hydrogen, fluorine, chlorine or bromine atom or for an α- or ß-position C_1-C_4 alkyl radical, whereby then $R^{6'}$ and R^7 represent hydrogen atoms, or else

$R^{6'}$ stands for a hydrogen, fluorine, chlorine or bromine atom or for a C_1-C_4 alkyl radical, whereby then $R^{6'}$ and R^7 represent a common additional bond,

R^7 stands for an α- or ß-position C_1-C_4 alkyl radical, whereby then R^6 and $R^{6'}$ represent hydrogen atoms, or else

R^6 and R^7 together stand for an α- or ß-position methylene group, and $R^{6'}$ stands for a hydrogen atom, or

R^6 and $R^{6'}$ together stand for an ethylene group or a methylene group, and R^7 stands for a hydrogen atom,

R^9 and R^{10} in each case stand for a hydrogen atom or a common bond,

R^{11} and R^{12} in each case stand for a hydrogen atom or a common bond,

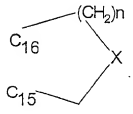
R^{13} stands for a methyl or ethyl group,

R^{15} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

R^{16} and $R^{16'}$, independently of one another, stand for a hydrogen atom, a C_1-C_3 alkyl radical or a C_2-C_4 alkenyl radical or together for a C_1-C_3 alkylidene group,

R^{15} and R^{16} stand for a common bond, and $R^{16'}$ stands for a hydrogen atom or a C_1-C_3 alkyl radical, or

R^{15} and R^{16} together stand for a ring of partial formula



in which n = 1 and 2, and X means a methylene group or an oxygen atom, and $R^{16'}$ stands for a hydrogen atom,

R^{171} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

R^{172} stands for a hydrogen atom, a C_1-C_3 alkyl radical, or a C_2-C_4 alkenyl radical,

$R^{171'}$ and $R^{172'}$ in each case stand for a hydrogen atom or for a common bond,

R^{21} stands for a hydrogen atom or a C_1-C_3 alkyl radical,

$R^{21'}$ stands for a hydrogen atom, a C_1-C_3 alkyl radical, or a hydroxy group.

3. Combination according to claim 2, whereby the gestagen is a (21S)-21-hydroxy-21-methyl-14,17-ethano-19-norpregna-4,9,15-triene-3,20-dione.

4. Combination according to one of the preceding claims, whereby the cyclodextrin is a ß-cyclodextrin.

5. Combination according to one of the preceding claims, whereby the cyclodextrin and the gestagen

are present with ß-cyclodextrin in a complex of 1:n (gestagen : cyclodextrin, $n \geq 1$), and

are present with γ-cyclodextrin in a complex of 1:n (n ≥ 1) (gestagen : cyclodextrin).

6. Combination according to one of the preceding claims as a pharmaceutical agent.

7. Combination according to claim 6 as a stable, oral formulation.

8. Combination according to claim 6 or 7 for the production of a pharmaceutical agent for treating menopausal symptoms.

9. Combination according to one of the preceding claims 1 to 5 for birth control.

10. Pharmaceutical agent or pharmaceutical preparation that contains a combination according to one of the preceding claims with pharmaceutically compatible adjuvants and vehicles.

11. Pharmaceutical agent or pharmaceutical preparation that contains a combination according to one of the preceding claims for peroral, oral, parenteral, transdermal, pulmonary, nasal, rectal, vaginal or intrauterine use.

12. Use of a combination according to one of the preceding claims 1 to 9 for the production of a medication for treating premenstrual symptoms, such as headaches, depression, water retention and mastodynia.

13. Process for birth control with administration of a combination according to one of claims 1 to 9.

14. Process for stabilization of a gestagen according to Formula I according to claim 2 with use of a ß-cyclodextrin or γ-cyclodextrin or derivatives of these cyclodextrins, which are

obtained by etherification or esterification of free alcoholic functions of cyclodextrins.

15. Process for complexing a gestagen according to one of claims 1 and 2 and a ß-cyclodextrin or γ-cyclodextrin while being triturated as a dry mixture or by precipitation reaction, preferably co-precipitation.

16. Process for direct pelletizing of a gestagen complex according to one of claims 1 and 2 with a ß-cyclodextrin or γ-cyclodextrin with the addition of pharmaceutically compatible adjuvants.

Attorney Docket Number: SCH 1808

DECLARATION FOR PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

COMBINATION OF GESTAGENES AND SUGARS

the specification of which

- ☐ is attached hereto
- ■ was filed on 13 OCTOBER 1999 as United States Application Number or PCT International Application Number PCT/EP99/07711 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
198 48 303	GERMANY	14 OCTOBER 1998	YES

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U.S.C. §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595); John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (37,432); Jennifer J. Branigan (40,921) and Robert E. McCarthy (46,044)

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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☐ Additional joint inventors are named on separately numbered sheets attached hereto.